LETTERS TO THE EDITOR

Intralaminar dural haematoma developing in the contralateral convexity after temporal lobectomy

A so called "subdural haematoma" actually develops in the dural border cell layer, which belongs to the dura; a true intralaminar dural haematoma to our knowledge has not been reported.

A 29 year old right handed man presented with a 14 year history of intractable epilepsy, which did not respond to major antiepileptic drugs. He usually felt an epigastric rising sense as an aura, then stared blankly, and showed oroalimentary automatism. Postictal confusion persisted for several hours. The frequency of attacks ranged from several times a month to several times a day, and he had been taking phenytoin, phenobarbitone, and vigabatrin. During childhood, he had had severe febrile seizures.

No neurological deficit was found on detailed physical examination. Brain MRI (1.5 T) disclosed bilateral hippocampal and diffuse cortical atrophy, and sharp waves were seen in the right anterior temporal region on interictal EEG. Prolonged video-EEG monitoring, however, showed sharp waves in the right temporal region and slowing in the left temporal region. Interictal single photon emission tomography (SPECT) did not show asymmetry between the two temporal lobes. Preoperative routine laboratory examination, including a coagulation study, showed no abnormality. Bilateral depth electrodes were inserted into both temporal lobes on 19 May 1995; postoperative CT showed no haematoma. After confirmation of right temporal onset, right temporal lobectomy and amygdalohippocampectomy were performed 10 days later. Postoperatively, the patient awoke fully and CT showed no unexpected findings. The following day, however, he became drowsy and CT showed an extra-axial haematoma in the contralateral convexity (fig 1). A diagnosis of epidural haematoma was made and he underwent emergency left frontoparietal craniotomy; The bone flap showed no penetration mark from the skeletal fixator used during the previous surgery. There was no haematoma in the epidural space. Incision of the visible dura showed blood clots, which were partially removed by suction; a yellow membrane, which also seemed to be dura, was noted at the bottom of the haematoma cavity. There was no active focus of bleeding. After removal of all the haematoma, it was apparent that this yellow membrane lined the entire cavity, and to expose the pial surface, this inner dura was incised. At the margin of the haematoma cavity, the covering and lining membrane was merged in a single layer, below which was the surface of the brain. Biopsy was performed at the margin, around which the two layered membranes merged to form a single layered dura. Because it adhered tightly, the underlying yellow membrane was difficult to dissect from the pial surface, and so was isolated and left in place. Concern about blood oozing from the undersurface of the covering membrane led to the removal of this membrane. Duraplasty was performed, using lyophilised cadaveric dura. The patient's postoperative course was uneventful, and he was discharged on the 7th postoperative day. Histological examination of the biopsy specimen showed separation of the dura and intralaminar dural haematoma (fig 2). There was no vascular malformation in the dura, but hippocampal sclerosis was found in the resected hippocampus. During two years of follow up, the patient remained seizure free without antiepileptic drugs.

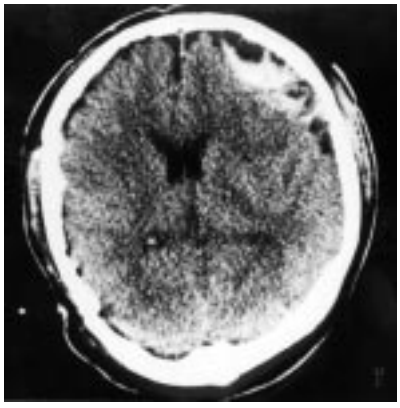

Figure 1 Computed tomogram obtained before the evacuation of intralaminar dural haematoma. Lobulated extra-axial haematoma is clearly visualised. The layering in the haematoma cavity, indicating an acute state, is not linear.

Cranial dura mater is a composite structure of cranial periosteum and dura propria; the second is composed of fibroblasts and a large amount of extracellular collagen, and the innermost part of the dura is formed by the dural border cell layer.[1] The dura-arachnoid junction, identified as the subdural compartment (dural border layer), consists of avascular tissue with flake-like, relatively electron lucent cells stacked in several layers with narrow intercellular clefts.[2] The dural border layer may be attached to the underlying arachnoid by an occasional cell junction. There is, however, no intervening space between the dural border cell layer and the arachnoid barrier cell layer that would correlate with what has been called the "subdural space." A survey of reports describing the morphology of the inner and outer capsule of so called subdural haematomas shows that dural border cells are found in both parts of the capsule.[1] These data support the view that what has been called a subdural haematoma is most often a lesion found within the layer formed by dural border cells.[1]

The reason for the postoperative delayed development of intralaminar dural haematoma contralaterally is unclear. Postoperative epidural haematomas developing contralaterally after supratentorial craniotomy have been reported.[3 4] The mechanism of this complication was reported to be unclear. In hydrocephalus, these massive epidural haematomas are probably caused by dura-skull detachment when the brain volume is strikingly reduced by a decompressive procedure. On rare occasions, pins from the head rest may detach the dura and cause epidural haematomas.[3]

In our case, however, there was neither hydrocephalus, nor penetration marks from the pins of the skeletal fixator. We used a negative pressure drainage system epidurally in this case, which might exert negative pressure intracranially. The inner surface of the dura and the pia-arachnoid were difficult to separate during surgery, indicating prior change at the dura-arachnoid junction. There is a possibility that the developing haematoma splits at the dural fibrous layer instead of at the dural border cell layer. To the best of our knowledge, this is the first report of a haematoma occurring between split dura propria.

This work was supported by Seoul National University Hospital Research Fund.

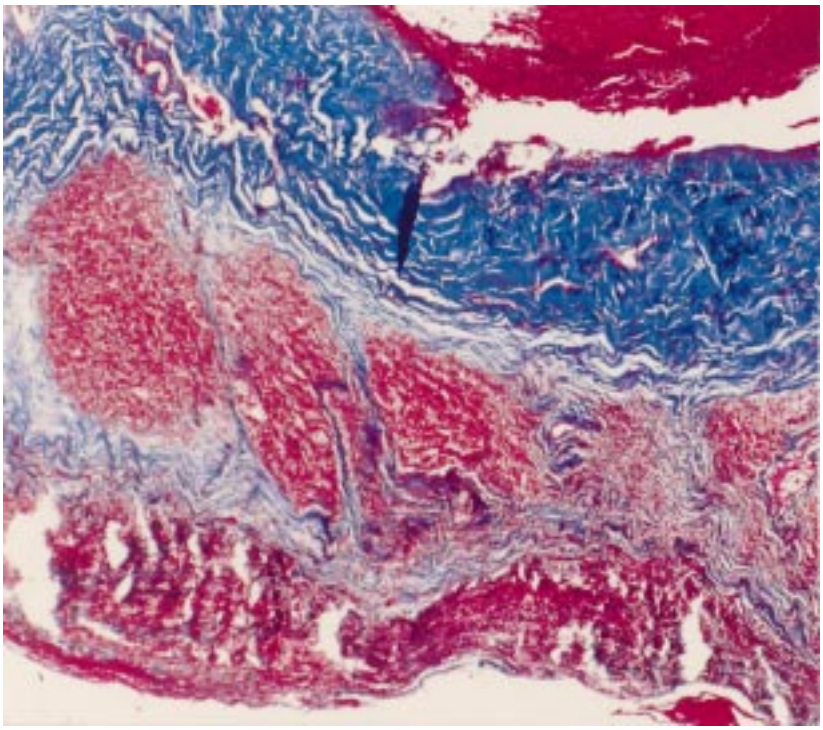

Figure 2 Photomicrograph shows separation of the dura propria and intervening haematoma. Masson's trichrome. Originally×200.

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Carbamazepine hypersensitivity syndrome presenting as vasculitis of the CNS

Carbamazepine is a drug widely used in the treatment of partial and generalised tonic-clonic seizures, trigeminal neuralgia and other pain syndromes, affective disorders, and paroxysmal symptoms of multiple sclerosis. Common side effects are diplopia, dizziness, headache, nausea, and rash. Less common side effects include blood dyscrasias, toxic hepatitis, hyponatraemia as a consequence of inappropriate antidiuretic hormone secretion, orofacial dyskinesias, and cardiac arrythmias.[1] Carbamazepine is also known to cause a severe systemic hypersensitivity reaction, known as carbamazepine hypersensitivity syndrome (CHS).[2] It consists of a triad of fever, lymphadenopathy, and rash; so called pseudolymphoma syndrome.[2] Other organs are often involved, most commonly the liver and, more rarely, lungs and kidneys.[3] There are two cases of meningitis described as a complication of the carbamazepine therapy.[4 5]

We describe a case of severe CHS with a typical pseudolymphoma picture and involvement of other organs, including the CNS. We suggest a possible pathogenetic mechanism for encephalopathy.

A 63 year old woman was started on carbamazepine (2×200 mg), as a seizure prophylaxis after a meningeoma operation. About 3 weeks later she developed a flu-like illness. Two days afterwards, she developed a generalised rash and facial oedema, and fever appeared. She was admitted to hospital where physical examination disclosed a diffuse purpuric rash, oedema of the face and the tongue, pharyngitis, enlargement of lymph nodes, and a raised body temperature (39.5°C). Laboratory data showed leucocytosis (45.1), eosinophilia (42%), and high C reactive protein (98).

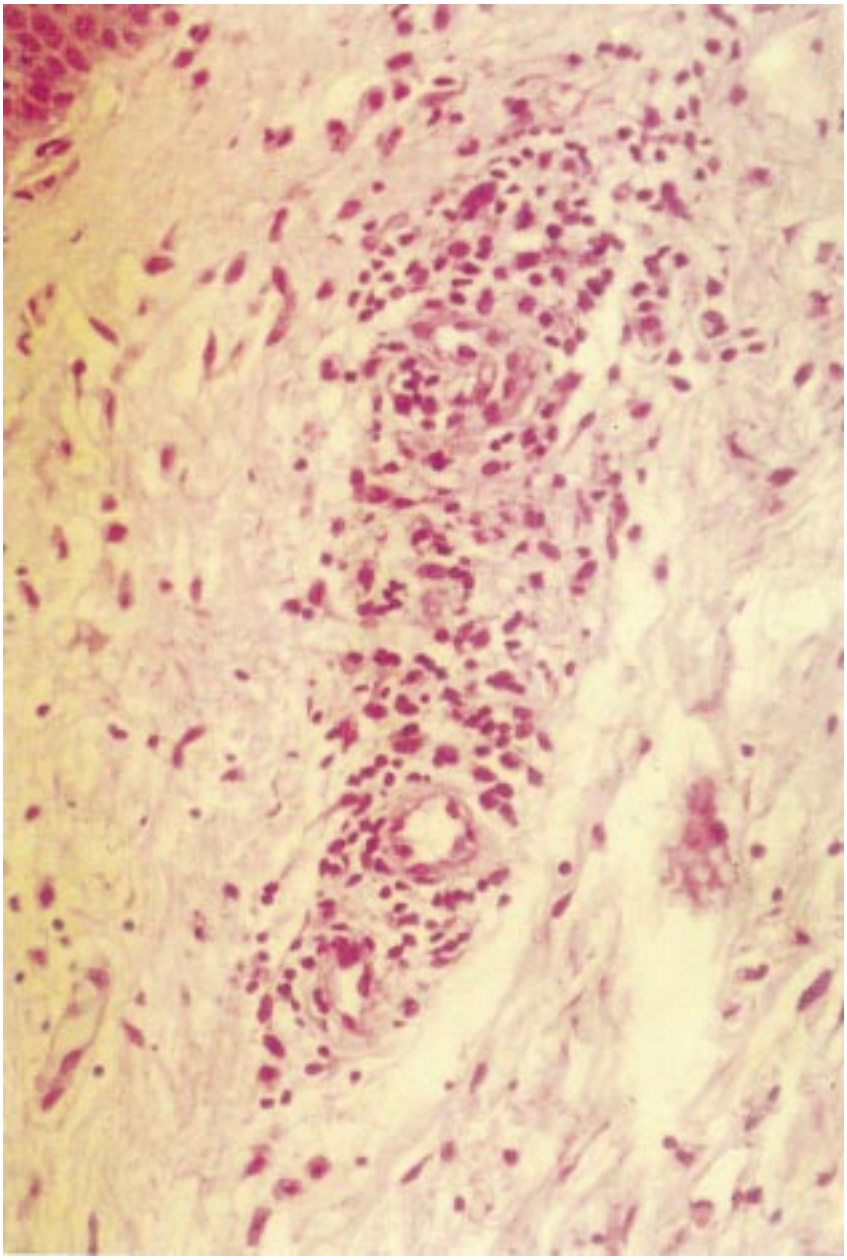
Liver enzymes were also raised. Additional tests disclosed a polyclonal increase in γ-globulin. Tests for Anti-DNA, anti-ENA, anti-ANA, and anti-ANCA antibodies were negative and complement C3 and C4 were normal. Chest radiography was normal, as well as lung function tests. Abdominal ultrasound investigation showed hepatosplenomegaly. Microbiological investigations failed to show any evidence of bacterial, fungal, viral, or parasitic infections. Skin biopsy showed vasculitis of small vessels with perivascular infiltrates of lymphocytes, monocytes, and macrophages (figure). The findings were compatible with an allergic reaction.

Carbamazepine was withdrawn and she was started on antibiotic treatment.

The patient's condition improved after the withdrawal of carbamazepine; the temperature fell, the lymph nodes regressed, the rash started to scale, and laboratory tests began to normalise. Antibiotic treatment was discontinued after a week.

Two weeks after admission and discontinuation of carbamazepine she became confused. Neurological examination disclosed cognitive deficits (mini mental state examination score 18), bilateral facial palsy of peripheral type, pyramidal (brisk reflexes, extensor plantar responses), extrapyramidal signs (rigidity, postural tremor), and ataxia. There was no neck stiffness and her temperature did not rise again. A lumbar puncture disclosed 211 cells/mm^3; more than 90% of them were lymphocytes. The concentration of protein in CSF was 1.29 mg/l and the concentration of sugar 2.85 mmol/l (40% of serum concentration). Concentrations of IgG, IgM, and IgA in CSF were raised. Oligoclonal bands were positive in serum and in CSF. Cultures for bacteria, fungi, and acid fast bacilli were negative, as were antibodies to mycoplasma, borrelia, and viruses. Serum and CSF VDRL and TPHA tests were negative. A T2 weighted MR image showed hyperintensive lesions in periventricular and white matter of the frontal and occipital lobes of both cerebral hemispheres. The lesions showed some opacification after injection of gadolinium contrast. There was no meningial enhancement.

A few days after the deterioration in the patient's condition she started to improve again. The skin lesions remitted completely



Dermal vasculitis of small vessels with abundant perivascular infiltrate of lymphocytes, monocytes, and macrophages..

and neurological signs slowly regressed. During her stay in hospital she received topical steroids on her skin lesions without other specific therapy. She did not experience an epileptic seizure.

To confirm the hypersensitivity to carbamazepine, we performed a patch test after the regression of the rash. The skin testing undoubtedly showed reactions to carbamazepine in four different concentrations of the drug.

On discharge about 2 months after the beginning of the disease she was left with subtle cognitive deficits (memory impairment). Her facial palsy, pyramidal and extrapyramidal signs, and ataxia resolved.

CHS is a severe systemic hypersensitivity reaction. It develops usually 1 week to 3 months after the introduction of the drug.[2] Blood tests usually show leucocytosis and eosinophilia; sedimentation rate may be raised.[2] Sometimes other organs are also affected. Liver involvement is very common; less often described are pulmonary disease, various types of renal diseases, and cardiac involvement.[6] Withdrawal of carbamazepine usually leads to rapid improvement of symptoms.

Our patient had a very severe hypersensitivity reaction to carbamazepine with typical pseudolymphoma syndrome, marked leucocytosis, eosinophilia, and raised liver enzymes. Our case is special in that 2 weeks after discontinuation of the drug, at the time of some clinical improvement, CNS symptomatology unexpectedly appeared. There are two cases described in the literature of a CHS associated meningitis. Both patients presented with high fever, stiff neck, and pathological CSF. In both of them symptoms and signs resolved shortly after the discontinuation of carbamazepine. Our patient did not have a raised temperature or meningism. She presented with cognitive deficits, bilateral facial palsy, pyramidal and extrapyramidal signs, and ataxia. Brain MRI showed multiple high signal lesions in the white matter. There was no meningial enhancement. Examination of the CSF disclosed a picture typical for lymphocytic meningioencephalitis. We excluded infectious, immunological, neoplastic, or paraneoplastic diseases which could present as our patient did and we confirmed hypersensitivity to carbamazepine with a patch test. Our patient showed slow improvement after CNS involvement and was left with mild residual cognitive impairment 2 months later on discharge.

There is no doubt that our patient presented with more severe CNS symptomatology than the previously reported cases. Oligoclonal bands in CSF matched by those in the serum are concordant with a severe systemic inflammatory reaction which resulted in breakdown of the blood-brain barrier. Considering the clinical picture, CSF and MRI findings, and results of skin biopsy, which showed vasculitis of the small vessels, we think that the pathogenetic mechanism behind encephalopathy is also small vessel vasculitis. We are aware that we needed to perform brain biopsy to confirm our hypothesis.

Carbamazepine is a frequently prescribed drug with wide indications of use. CHS is one of its most severe complications, but fortunately it is very rare. There are 25 cases described in the literature.[3 6] Our patient started with clinical features typical of the syndrome and this was later complicated by an encephalopathic picture, which is very rare. We emphasise the unusual course of the disease; the flare up of the CNS symptomatology after the discontinuation of the drug, and some initial improvement. We suggest that the pathogenetic substrate for encephalopathy may be small vessel vasculitis.

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Thalamotomy for severe antipsychotic induced tardive dyskinesia and dystonia

The case described by Weetman *et al*[1] confirms the difficulty in managing drug induced (tardive) dyskinesia and dystonia, and suggests that posteroventral pallidotomy should be considered as a possible treatment option for this condition.

We report on a patient with similarly severe and refractory drug induced dystonia, and dyskinesia who responded to a right thalamotomy, a potentially safer surgical procedure than pallidotomy.[2 3]

A 66 year old right handed, retired newsagent had a long history of a bipolar affective disorder beginning at the age of 25 years. He had been treated with a combination of tricyclic antidepressant drugs, antipsychotic drugs, lithium carbonate, and electroconvulsive therapy. In 1993 his medication was changed from 25 mg thioridazine thrice daily to 2 mg trifluoperazine thrice daily (because of postural hypotension). Two months later the patient started to complain of abnormal neck movements associated with facial grimacing and neck pain. He was referred to a neurologist who diagnosed drug induced dystonia and dyskinesia of the head and neck and he was started on 5 mg benzhexol four times a day with no effect.

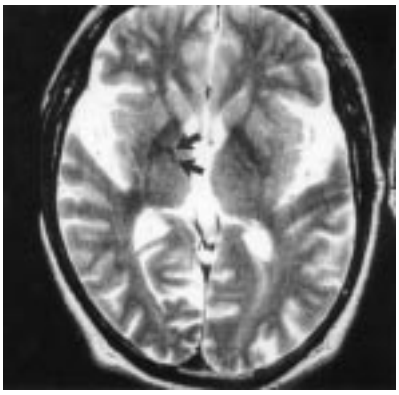
In 1995 neurological examination disclosed orofacial dyskinesia and torticollis to the left with hypertrophy of the right sternocleidomastoid muscle. He experienced stereotyped movements of the head and neck in a "no no" fashion and dystonic posturing of the left arm. Progressive torticollis and twisting of the trunk were features that confined him to bed. He scored 36/40 on the abnormal involuntary movements scale (AIMS).[4] There were no other abnormal signs. Normal investigation included routine full blood count, urea and electrolytes, liver function tests, serum and urinary copper, caeruloplasmin, venereal disease research laboratory test, and a Huntington's trinucleotide repeat genetic analysis.

Protein electrophoresis showed an IgG paraproteinaemia but subsequent Bence Jones protein, skeletal survey, bone marrow aspirate, and trephine were normal. A CT of the head under general anaesthetic was normal. Sulpiride was cautiously introduced with an initial transient benefit; subsequent longer term treatment was unhelpful. Botulinus toxin injections were introduced at regular 3 monthly intervals with moderate effect. By January 1997 he was obtaining no relief of symptoms from botulinus injections or 200 mg sulpiride twice daily. Alternative therapies were tried and these included clonazepam, diazepam, nitrazepam, and tetrabenazine all at 125 mg thrice daily, co-careldopa at 25 mg thrice daily, and olanzapine at 15 mg once daily. Because of his Ig G paraproteinaemia he received 1.5 g methylprednisolone for 5

Electrode tip positions and stimulation profiles were as follows

Lesion position	*Stimulation profile*		
Lesion 1:			
(a) 11 mm posterior to FM	2 Hz	Motor response hand, face	5.5 V
13 mm lateral to midline	50 Hz	Sensory response cheek, hand	5 V
		Driving dystonia hand and torticollis	7 V
(b) 14mm posterior to FM	2 Hz	Motor response	
13mm lateral		Hand	5 V
		Neck	6 V
	50 Hz	Driving dystonia hand	4 V
		Sensory response hand	4.5 V
		Inhibiting motor foot	5 V
Lesion 2:			
(a) 14 mm posterior to FM	2 Hz	Motor response hand, face	5.6 V
7 mm lateral	50 Hz	Sensory response hand, face, foot	3.8 V
		Driving dystonia hand	5.0 V
(b) 17 mm posterior to FM	2 Hz	Motor response hand	3.5 V
10 mm lateral		Driving head movement	4.0 V
		Motor response face	5.0 V
	50 Hz	Sensory response	
		Hand	1.0 V
		Face	2.4 V
		Driving head movement and hand	3.4 V

Lesion 1 was mainly in Vim. Lesion 2 was mainly in VPM (and VPL?) but probably included part of the centromedianum-parafasicular complex.[5]
All lesions were made on the foramina of Monro-posterior commissure (FMPC) plane. FM-PC distance measured 27.5 mm and the macrostimulation profile showed the thalamus to be relatively narrow. Each lesion was double; two adjacent lesions were made on each occasion.



Postoperative MRI confirming the position of stereotaxic lesions in the right thalamus (black arrows).

days with no symptomatic effect or objective change in his AIMS score.

In April 1997 ventral thalamotomy was performed on the right side in two stages under local anaesthesia. A Bennett spheroid guide had previously been inserted under general anaesthesia using CT guidance and a Leksell frame. Details of the lesions are shown in the table. The first lesion was relatively anterior and it reduced the torticollis, neck pain, hypertonia, and the dyskinesia of the contralateral limbs and allowed him to smile and laugh. One week later a second lesion was placed posteriomedial to the first. This abolished the residual "cogwheeling" of the left upper limb and improved his dexterity. There were no surgical complications. Postoperative MRI (figure) 8 months after the procedure confirms the position of the two lesions in the right thalamus.

Twelve months later the patient remains well with minimal dystonic neck movements and no evidence of abnormal posturing of the left arm and off all medication. His AIMS score is now 8/40.

Although the efficacy of thalamotomy has long been recognised in secondary dystonia[6] we are not aware of any reports of its use in drug induced dystonia. The mechanism of drug induced dystonia is not yet known and extrapolating the surgical results for treatment of dystonia of other aetiologies may not be appropriate. The reported mortality from thalamotomy ranges from 0.4% to 6%.[2] Recent experience with pallidotomy indicates an incidence of severe clinical complications of between 2%-8%.[2] Because of the proximity of the optic tract to the globus pallidus persistent visual defects are a well known risk of pallidotomy, up to 14% in one series.[3] It is too early to be certain of long term efficacy but 12 months after operation the patient remains well and off all medication. We conclude that thalamotomy should also be considered in patients with medically refractory drug induced tardive dystonia and dyskinesia.

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Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial

Painful neuropathy is a common and disabling problem in patients with longstanding diabetes mellitus. Tricyclic antidepressant drugs and other chronic analgesics have been beneficial in some patients,[1] but no agent successfully relieves pain in most patients and adverse effects often preclude their use in high doses. Anecdotal reports suggest that gabapentin ameliorates pain associated with neuropathy and other neurological conditions with few side effects.[2 3] We conducted a randomised, double blind, placebo controlled trial to study the effect of low dose gabapentin in patients with painful diabetic neuropathy.

We recruited 40 patients with painful diabetic neuropathy who had (1) diabetes for at least 6 months on a stable dosage of insulin or oral hypoglycaemic agent, (2) distal symmetric sensorimotor neuropathy as shown by impaired pin prick, temperature, or vibration sensation in both feet and absent or reduced ankle reflexes, and (3) daily neuropathic pain in the acral extremities, of at least moderate severity, for over 3 months that interfered with daily activity or sleep. Excluded were those with diabetes and chronic renal insufficiency, painful diabetic plexopathy, or lumbosacral polyradiculopathy, peripheral vascular disease, another painful condition, or other cause for neuropathy. Patients were randomly assigned to gabapentin (300 mg capsules) or placebo for 6 weeks (phase I) followed by a 3 week washout period and then crossover (phase II). The dose of gabapentin or placebo was increased by one capsule every 3 days to a stable dosage of one capsule three times daily (900 mg/day) that was maintained throughout the remainder of the treatment period. The low dosage of gabapentin was chosen to minimise adverse effects that might compromise blinding. Treatment with stable dosages of nonsteroidal anti-inflammatory agents or narcotics were permitted during the trial but patients discontinued all other chronic analgesic medications 3 weeks before study entry.

At the beginning and end of each treatment period, patients rated their level of pain over the preceding 24 hours on a 10 cm visual analogue pain scale (VAS), ranging from 0 ("no pain") to 10 ("worst pain ever"). Present pain intensity (PPI, "rate how much pain you have at this moment," using a similar 0–10 scale) and the McGill pain questionnaire (MPQ) were recorded at the initial and final visits of each treatment period.[4] At the end of each treatment period patients provided a global assessment of pain relief: none, mild, moderate, or excellent, as compared with the level of pain preceding each treatment period. The global assessment of pain relief was dichotomised (none/mild *v* moderate/excellent) for purposes of analysis. The protocol was approved by the Institutional Review Board at St Elizabeth's Medical Center and all patients gave written informed consent.

There were 31 men and nine women, with an average age of 62 years (SD 10.9 years, range 43–82 years). All but one had adult onset diabetes mellitus, with a mean duration of 14 years (SD 9.9 years, range 6 months-40 years). Ten had neuropathic pain limited to the feet, 19 had pain in the feet and legs, and 11 had pain in the feet, legs, and hands. The mean duration of neuropathic pain was 4 years (SD 3.5 years, range 4 months-15 years). Twenty five had previously used narcotics or other chronic analgesics to manage their pain.

Nineteen patients were randomised to the active drug and 21 to placebo during the first treatment period. The mean reduction in the MPQ score was 8.9 points with gabapentin compared with 2.2 points with placebo (p=0.03, two sample *t* test). There were no differences in the mean change of the VAS or PPI scores between gabapentin and placebo (table). Fourteen patients reported moderate or excellent pain relief with gabapentin only, six with placebo only, and three with both; 17 reported none or mild relief after both treatments (p=0.11, McNemar's test). There were no serious adverse events. Adverse effects were significantly more common with gabapentin (12 patients) compared with placebo (four patients, p<0.001, McNemar's test). The most common side effects of gabapentin were drowsiness (six patients), fatigue (four), and imbalance (three). All adverse effects resolved promptly after discontinuation of the drug.

Anecdotal reports suggest that gabapentin has beneficial effects in patients with various painful neurological conditions, including HIV neuropathy,[2] postherpetic neuralgia,[2] and reflex sympathetic dystrophy.[3] The mechanism of action of gabapentin in ameliorating pain is unknown, but animal studies suggest that its pain modulating properties may be linked to the release of the neuro-

Comparison of mean change in pain scales between gabapentin and placebo

Pain scale	*Gabapentin*	*Placebo*	*Difference*	*p Value*
MPQ	8.9 (2.3)	2.2 (2.2)	6.7 (3.2)	0.03
VAS	1.8 (0.5)	1.4 (0.3)	0.4 (0.6)	0.42
PPI	1.2 (0.4)	0.3 (0.5)	0.9 (0.7)	0.2
No of patients reporting moderate or excellent pain relief*	17	9		0.11

*Global assessment of pain relief.
MPQ=McGill pain questionnaire; PPI=present pain intensity; VAS=visual analogue scale; numbers in parentheses are SD.

transmitter GABA in spinal cord pathways that modify pain perception.[5]

There was statistical improvement in only one of four end points, the MPQ score, with gabapentin compared with placebo. The MPQ is a valid, consistent, and reliable measure of subjective pain experience, and usually correlates with other measures of pain intensity, including the VAS and PPI scales.[4] We designed the study to have an 80% power to detect a 20% reduction in pain scores, reflecting a modest but clinically important improvement. The mean change of the VAS and PPI scales and the patient's global assessment of pain relief were not significantly different from placebo. We used a crossover design because of its statistical efficiency, but the MPQ and VAS scores did not return to baseline after crossover in patients who received gabapentin in phase I (the washout period was inadequate); therefore, we may have underestimated improvement with gabapentin in the VAS scale that may have been detected using a parallel group design. Furthermore, a limitation of our study was that quantitative measures (for example, nerve conduction studies, quantitative sensory thresholds) were not used to further characterise the type of neuropathy. Because of the heterogeneous nature of neuropathic pain in our study patients, we may not have identified a subset of patients who improved with gabapentin. Alternatively, the dosage of gabapentin may have been too low to induce analgesia in patients with painful diabetic neuropathy, although similar regimens have been reported to be effective in patients with other painful conditions.[2 3]

The results of this study suggest that gabapentin is probably ineffective or only minimally effective for the treatment of painful diabetic neuropathy at a dosage of 900 mg/day.

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Single motor unit activity pattern in patients with Schwartz-Jampel syndrome

Two sisters, 9 and 11 years old, with typical clinical symptoms of Schwartz-Jampel syndrome were investigated. Conventional electromyographic investigation with concentrical needle electrodes in the biceps brachii and tibialis anterior showed continuous muscle activity (myotonic burst, high frequency discharges of single motor units with "bizarre" rhythmic activity). The single motor unit action potential (MUAP) was studied in detail by monopolar surface selective electrode with a small leading off area. The pattern suggests that the muscle membrane alone is the not the only reason for abnormality.

Continuous muscle activity is a prominent symptom in patients with Schwartz-Jampel syndrome. Some authors maintain that this may originate in the nerve or end plate. Lehmann-Horn *et al*[1] showed two muscle membrane abnormalities by voltage clamp and patch clamp techniques and concluded that spontaneous activity in the Schwartz-Jampel syndrome originated in the muscle membrane itself. Arimura *et al*[2] found a normal end plate function and assumed that the motor unit pattern influenced interdischarge interval changes. It is difficult to make a precise analysis of the MUAPs with concentric needle electrodes because of other interfering spontaneous activities. Thus a monopolar surface selective electrode with a small leading off area[3] was employed to obtain a more precise assessment of a single MUAP pattern.

The patients were two sisters, 9 and 11 years old, from consanguineous parents. They displayed short stature, bone deformities (kyphoscoliosis, pigeon breast, short neck, pes equinovarus), facial dysmorphism, muscle stiffness, and missing tendon reflexes in the lower limbs. Concentric needle EMG was performed when the patients were 7 and 9 years old and disclosed abnormality. The needle insertion, mechanical stimulation, and mild muscular contraction induced spontaneous activity. Myotonic discharges (fig 1 A and B) were found in all examined muscles (abductor digiti minimi, quadriceps femoris, tibialis anterior, biceps brachii).There were also spontaneous high frequency biphase potentials. Some of the high frequency discharges appeared as doublets or complex repetitive discharges. Routine nerve conduction studies (motor conduction velocity, distal latency, compound muscle action potentials, and sensory action potentials in upper and lower limbs) were normal.[4] Electromyographic investigations of single MUAPs were performed in biceps brachii and tibialis anterior muscles. Involuntary motor unit activity was recorded by monopolar surface selective electrode with a small leading off area[3] for 30 minutes. A Mistro 5+electromyograph and a Teac type recorder were employed to register the action potentials. Distance between the negative peaks of MUAP was measured with a resolution of 0.1 ms. After applying these electrodes we found single MUAP trains between myotonic discharges. They showed without provoking a burst of activity, as usually happens during needle electromyography.

Motor unit firing began with doublet discharges (fig 2 trace 1). After a few seconds MUAP alternated between doublets and triplets (fig 2 trace 2). and then the motor unit fired with stable triplets (trace 3). Similarly, triple discharges turned into quadruplets, and then multiplets (traces 4 to 11) and the number of firing impulses increased at the end of motor unit discharge. All multiplet impulses were similar in shape.

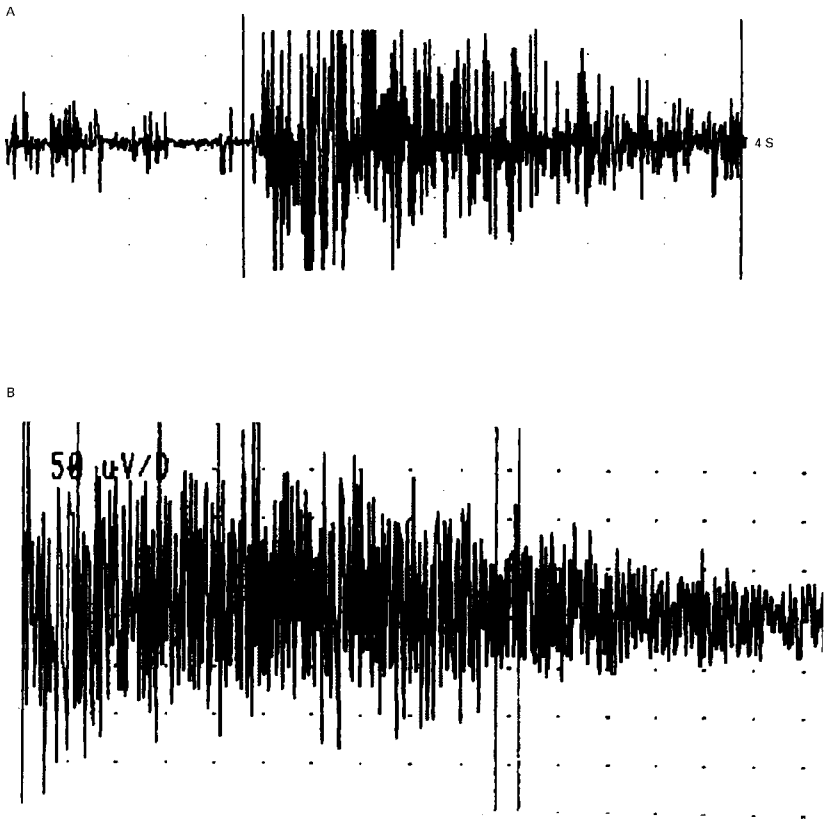

Figure 1 Myotonic discharge recorded by monopolar surface electrode with a small leading off area (A) and needle electrode (B) from biceps brachii muscle.

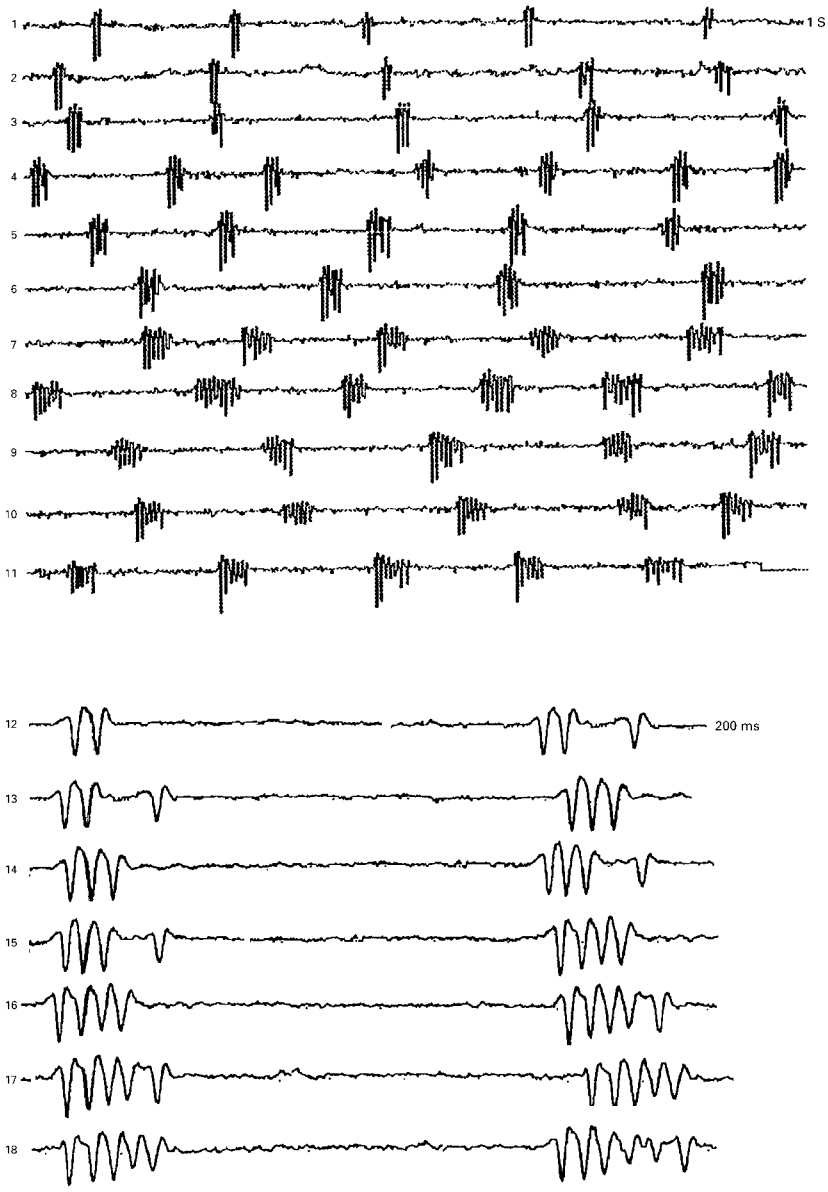

Figure 2 Firing pattern of a single motor unit in involuntary activity. The beginning of the firing is shown on the first trace and the end on the 11th trace. The time duration from trace 1 to 11 is 1 s and from trace 12 to 18 is 200 ms.

Amplitude of the second impulse in the doublet was lower or higher than the amplitude of the first impulse (fig 2 trace 1). Amplitude of the second impulse in the triplet was predominantly lower than that of the first impulse but could also be higher (traces 2 and 3), whereas amplitude of the third impulse varied depending on the interimpulse interval, and was higher after a larger interimpulse interval. Other multiple discharges followed the same pattern. At the end of motor unit firing, the amplitude of successive impulses smoothly decreased (traces 10 and 11).

Every successive change in the number of impulses in a train was marked by a longer interval between the latest impulse of the train and the "new" impulse. With the increase of the number of impulses in the train, the interval before the emergence of a "new" impulse decreased (fig 2 traces 12 to 18). Interimpulse interval in the multiplets had a latency of 2 to 10 ms. The phenomenon was found in both sisters.

Electrophysiological studies of patients with the Schwartz-Jampel syndrome (normal nerve conduction, spontaneous activity myotonic discharge) have implied that spontaneous activity originates in the muscle membrane. The single MUAP pattern of repetetive neuronal discharges, however, suggests that a defect in the muscle membrane is not the only reason of abnormality. The MUAP pattern found supposes an influence at a higher level than the muscle. Multiplet discharge with an interimpulse interval of 2 to 10 ms probably originated in the muscle membrane but the increasing number of impulses in multiplets and the long intermultiplet intervals cannot be explained simply by the known abnormalities of the muscle membrane. Moreover, doublet, triplet, and multiplet electromyographic phenomena are neuromyotonic. In our opinion the reasons for the abnormality are complex and not yet understood.

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Transient severe parkinsonism after acute organophosphate poisoning

Acute poisonings with organophosphate pesticides occur often. The acute phase is characterised by muscarinergic (miosis, bradycardia, hypotension, dyspnoea, cyanosis, salivation, vomiting, and diarrhoea) and nicotinergic symptoms (fasciculations, cramps, paralysis) as well as multiple central nervous manifestations (headache, anxiety, generalised weakness, confusion, convulsion, and coma) caused by an irreversible inhibition of acetylcholinesterase (AChE). In some patients the acute cholinergic crisis is followed by an intermediate syndrome characterised by weakness of proximal limb muscle, neck flexors, and respiratory muscles and paralysis of motor cranial nerves due to a neuromuscular junctional defect. A delayed polyneuropathy manifested as distal motor polyneuropathy may appear 2 to 3 weeks after poisoning.[1]

In addition, a limited number of case studies are available describing extrapyramidal manifestations after acute organophosphate poisoning such as dystonia,[1 2] rest tremor,[2] cog wheel rigidity,[2] and choreoathetosis.[2–4] Only one study describes a case of possible organophosphate induced parkinsonism. However, there was no clear relation between poisoning and extrapyramidal symptoms due to chronic organophosphate exposure and, in addition, numerous episodes of acute intoxication.[5]

To our knowledge, no patient has previously been documented presenting with the complete picture of transient severe parkinsonism including bradyphrenia, rigidity, rest tremor, akinesia, impairment of speech and swallowing, and salivation after acute organophosphate intoxication and, in addition, having a marked improvement after treatment with amantadine.

The 56 year old male patient ingested an unknown dose of the organophosphate demeton-S-methyl-sulphone (Metasystox R) in a suicide attempt. He was admitted to the intensive care unit with unconsciousness, cyanosis, dyspnoea, miosis, bradycardia, and hypotension and required mechanical ventilation. Plasma cholinesterase (PChE) was less than 1%. He was treated with obidoxime and atropine (14 days) and haemoperfusion was

carried out four times. On day 6, the patient regained consciousness but remained immobile and confused. Neurological examination on day 7 disclosed a positive Babinski's sign and bilateral hyperreflexia. On day 8, rigidity of all limbs, akinesia, and rest tremor of about 6 Hz in both hands were noticed for the first time. Therefore, the diagnosis of diffuse hypoxic encephalopathy was suspected but on day 10 pyramidal signs disappeared. On day 11, the concentration of PChE reached the normal range. The same day the patient was taken off mechanical ventilation but because of persistent salivation, disturbance of swallowing, and consecutive aspiration it was needed again for 24 hours. Even after complete pulmonary and cardiovascular stabilisation the patient remained completely immobile, unable to turn around in bed or to speak. Because rigidity, tremor, akinesia, and bradyphrenia persisted on day 24 the diagnosis of parkinsonism was suspected and treatment with amantadine intravenously (300 mg/day) was started. Within 1 day there was marked improvement of consciousness, orientation, mobility, and speech. Furthermore, salivation, and disturbance of swallowing improved and, therefore, feeding by tube was no longer necessary. Only 6 days later, on day 30, the patient left the intensive care unit and moved to the neurological department. Due to a continuous improvement treatment with amantadine was stopped on day 40. After discontinuation no relapse occurred. When the patient was discharged on day 61 he had completely recovered from parkinsonian symptoms.

Between day 33 and day 53 various additional diagnostic examinations such as MRI, [^{18}F]-fluorodesoxyglucose-positron emission tomography ([^{18}F]-FDG-PET), [^{18}F]-fluorodopa-PET ([^{18}F]-F-DOPA-PET) and [^{123}I]-iodobenzamide-single photon emission computed tomography ([^{123}I]-IBZM-SPECT) were performed but showed no pathological findings. In addition, on clinical examination and electrophysiological studies there were no signs of an intermediate syndrome or delayed polyneuropathy. Furthermore, the patient had no history of parkinsonism and antidopaminergic therapy, and family history was unremarkable.

This is a description of a patient who developed the complete picture of severe parkinsonism after acute OP poisoning with demeton-S-methyl-sulphone, an S-substituted phosphorothiate. Parkinsonian symptoms were noticed 8 days after intoxication, markedly improved after treatment with amantadine, and resolved spontaneously within 9 weeks.

We suggest that parkinsonism was due to a transient pharmacological effect. Organophosphate poisoning causes irreversible AChE inhibition resulting in raised acetylcholine (ACh) concentrations. The striatum contains large aspiny cholinergic interneurons which are likely to stimulate efferent enkephalin-containing GABA projections to the globus pallidus externus leading via increased glutaminergic excitation in the subthalamic nucleus to a reduced cortical glutamate stimulation (indirect pathway of the corticostriatopallidothalamocortical circuit). Therefore, it can be speculated that reduced striatal AChE activity resulted in a decrease of cortical glutamate stimulation which clinically mimicked a dopamine deficiency syndrome. This hypothesis is supported by the fact that the patient recovered completely and no relapse after discontinuation of amantadine medication occurred. Amantadine was preferred to other antiparkinsonian treatment because there was no evidence for a dopamine deficiency and, furthermore, can be administered intravenously. The benefit of amantadine might be due to its antiglutaminergic effect in the subthalamic nucleus as well as its presumed NMDA receptor mediated antagonism on ACh release on striatal interneurons.

We looked for various alternative explanations for the presented parkinsonism. In MRI, however, there were no hypoxic lesions and [^{18}F]-FDG-PET disclosed normal striatal glucose metabolism. [^{18}F]-F-DOPA-PET and [^{123}I]-IBZM-SPECT did not show a reduction of presynaptic striatal F-DOPA uptake or a decrease of postsynaptic dopamine D2 receptor capacity. Therefore, it seems to be very unlikely that parkinsonism in this patient was due to hypoxic encephalopathy, idiopathic Parkinson's disease, or postsynaptic dopaminergic changes.

Although acute organophosphate poisoning is relatively common only a few case studies are available describing central nervous symptoms suggesting an involvement of the extrapyramidal system. Extrapyramidal manifestations were noticed early in the course of the disease and spontaneously disappeared within a few weeks in those patients who survived.[1–4] Therefore, it can be speculated that such symptoms will often be overlooked or will be masked by other complications. So far it is unclear whether the occurrence of extrapyramidal symptoms depends on the type of the organophosphate agent or on the severity of poisoning.

In conclusion, transient parkinsonism must be added to the sequelae of acute organophosphate poisoning persisting even after cholinergic symptoms have resolved. Although parkinsonian symptoms spontaneously improved the diagnosis should not be missed because complications such as aspiration, pneumonia, thrombosis, and prolonged mechanical ventilation could be prevented by appropriate treatment.

We thank Professors WH Knapp, Department of Nuclear Medicine, Medical School Hannover, and KL Leenders, Paul Scherrer Institut, Villingen, Switzerland, for carrying out [^{18}F]-FDG-PET, [^{123}I]-IBZM-SPECT, and [^{18}F]-F-DOPA-PET, respectively.

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Oropharyngeal palsy in Guillain-Barré and Fisher's syndromes is associated with muscle weakness in the neck and arm

Guillain-Barré syndrome is an immune mediated peripheral neuropathy characterised by acute onset of symmetric limb weakness and areflexia. Patients with typical Guillain-Barré syndrome had greater leg weakness than arm weakness, with an ascending progression.[1] Some patients with Guillain-Barré syndrome, however, present muscle weakness only at the oropharynx, neck, and proximal upper limb muscles, and a descending pattern of weakness appears as illness progresses.[2] Ropper[2] proposed that the second group of patients had a variant of Guillain-Barré syndrome, "pharyngeal-cervical-brachial weakness (PCB)". Ophthalmoplegia and cerebellar ataxia, however, are often noted in patients with PCB. Therefore, it is unclear whether PCB is an "atypical" Fisher's syndrome or a distinct variant entity of Guillain-Barré syndrome. To clarify this, we investigated the relation of neck and limb weakness with cranial nerve involvements. We report here that oropharyngeal palsy in Guillain-Barré syndrome has a significant association with neck and arm-dominant weakness whereas ophthalmoplegia does not.

We made prospective examinations of 113 patients with Guillain-Barré syndrome and 39 patients with Fisher's syndrome who had been referred to our neuroimmunological laboratory between December 1996 and February 1998 with cranial nerve dysfunction and weakness in the neck and limbs on the day of admission. All the patients fulfilled the accepted clinical criteria for these syndromes. Diagnosis of Fisher's syndrome was also made in patients who initially presented with ophthalmoplegia, ataxia, and areflexia and later developed generalised muscle weakness. On admission, 53 patients with Guillain-Barré syndrome or Fisher's syndrome (Guillain-Barré syndrome, 14 (12%); Fisher's syndrome, 39 (100%)) had ophthalmoplegia, and 48 (Guillain-Barré syndrome, 41 (36%); Fisher's syndrome, seven (18%)) had oropharyngeal palsy. Generalised muscle weakness was present in six (15%) patients with Fisher's syndrome. Of the 48 patients with Guillain-Barré syndrome or Fisher's syndrome who had oropharyngeal palsy, 36 (75%) and 20 (42%) respectively had neck and arm-dominant weakness, compared with 33 (32%) and 13 (13%) of the 104 patients without oropharyngeal palsy (table). Patients with oropharyngeal palsy showed a significant increase in the frequency of neck weakness (χ^2 test, $p<0.0001$) and arm dominant weakness ($p<0.0001$). By contrast, leg dominant weakness was less common in patients with oropharyngeal palsy (11 (23%)) than in patients without (50 (48%)) ($p=0.003$). There was no significant association of ophthalmoplegia with neck or arm dominant weakness ($p=0.5$ and $p=0.9$ respectively).

Statistical analysis showed that muscle weakness in the neck and upper limbs was frequent in patients with Guillain-Barré syndrome or Fisher's syndrome who had oropharyngeal palsy. This may account for the distribution of muscle weakness that occurs in PCB. According to the clinical criteria of Ropper *et al* for PCB,[1] it should be diagnosed

Relation of oropharyngeal palsy to neck and limb weakness in Guillain-Barré and Fisher's syndromes

	Oropharyngeal palsy				
	Present (n=48)	Absent (n=104)	p Value	Odds ratio	95% CI
Ophthalmoplegia	18 (38%)	35 (34%)	0.6		
Neck weakness	36 (75%)	33 (32%)	<0.0001	6.5	3.1–13.6
Arm dominant weakness	20 (42%)	13 (13%)	<0.0001	5.0	2.3–10.9
Leg dominant weakness	11 (23%)	50 (48%)	0.003	0.3	0.1–0.7

Differences in proportions were examined by χ^2 test. 95%CI=95% confidence interval.

only in patients who have a restricted distribution of muscle weakness in the pharynx, neck, and proximal upper limbs but no weakness or areflexia in the legs. In his original report,[2] however, one of the three patients with PCB had generalised areflexia. Moreover, the patient with Guillain-Barré syndrome described by Mizoguchi *et al*,[3] whose initial symptoms were lower cranial nerve dysfunction and upper limb weakness, later developed generalised muscle weakness. These patients with PCB with generalised areflexia or weakness indicate that the preservation of the tendon reflex and muscle power in the legs depends on the severity of the involvement of the limbs. None of the patients in our study met the clinical criteria proposed by Ropper.[1] However, the close association of weakness of the pharynx, neck, and upper limbs in Guillain-Barré syndrome and Fisher's syndrome indicates that PCB is a distinct variant of Guillain-Barré syndrome, because ophthalmoplegia, a cardinal sign in Fisher's syndrome, is not associated with oropharyngeal palsy, neck weakness, or arm dominant weakness.

Our finding is also supported by detection of serum antibodies against GT1a ganglioside in patients with PCB which show different reactivity from those in patients with Fisher's syndrome.[3 4] IgG anti-GT1a antibodies in patients with PCB are not absorbed by GQ1b ganglioside whereas those in patients with Fisher's syndrome are.[4] Because only GT1a is recognised by serum IgG from the patient who had a restricted distribution of muscle weakness in the pharynx, neck, and proximal upper limbs,[4] we speculate that anti-GT1a and anti-GD1a antibodies respectively contributed to the development of PCB and generalised weakness in the patient described by Mizoguchi *et al*.[3]

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Cumulative meta-analysis of aspirin efficacy after cerebral ischaemia of arterial origin

In 1996 we reported in this *Journal* that there was virtually no difference in relative risk reduction for low (<100 mg/day), medium (300 to 325 mg/day), and high (>900 mg/day) doses of aspirin in the prevention of vascular events in patients with cerebral ischaemia of arterial origin.[1] A meta-analysis of the cumulative data showed a modest 13% (95% confidence interval (95% CI) 4% to 21%) relative risk reduction. Recently the final data of the second European Stroke Prevention Study (ESPS-2) were reported.[2] One of its comparisons was between 50 mg aspirin daily and placebo in patients after cerebral ischaemia; the relative risk reduction of 13% (95% CI 0% to 24%) was exactly the same as that resulting from our previous meta-analysis. This similarity allows the calculation of an update of the meta-analysis. The overall relative risk reduction of course remains 13%, but the 95% CI has narrowed to 6% to 19%. The figure shows the results of the updated cumulative meta-analysis, in chronological order. These data once more underscore the need for more efficacious treatment strategies. For this reason we started the European and Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT).[3]

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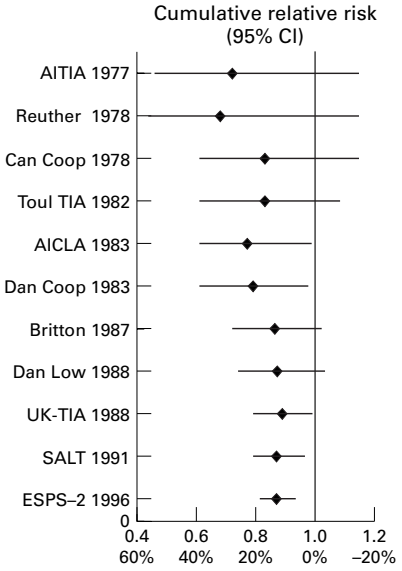

Cumulative meta-analysis in chronological order (1977 to 1996) with relative risks and corresponding relative risk reductions with 95% CIs. Each line represents the relative risk and 95% CI of that study combined with all previous studies.

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CORRESPONDENCE

Hemifacial spasm

We have looked with interest at the scan of a patient with hemifacial spasm by Reigosa and Rios.[1] Indeed, this is a very nice MRI which shows an arterial loop and the internal auditory meatus. However, this loop is not the cause of hemifacial spasm.

Typical hemifacial spasm, which begins in the orbicularis oculi and gradually progresses down the face, is caused by a blood vessel on the non-fascicular portion of the facial nerve on the caudal or anterior aspect, including the intrapontine nerve. Atypical hemifacial spasm, which starts in the buccal muscles and progresses up the face, is caused by a blood vessel on the posterior or rostral side of the nerve. This is much less common. The compression is also at the brainstem. A distal artery, as shown in the scan, does not cause hemifacial spasm. The syllogism that Reigosa and Rios bring out—namely, that botulinum toxin helped and that this picture showed the pathology, is inadequate. They do not have a completed explanation.

This patient's spasm will recur because the cause has not been treated. The spasm has an excellent chance of responding to a microvascular decompression of the facial nerve performed by a neurosurgeon who has experience in the nuances of the operative procedure.

Nevertheless, Reigosa and Rios have shown a beautiful scan.

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Pego Reigosa replies:

We thank Jannetta and Kassam for their interest in our article.[1] We think that the vascular loop that appears in the MR image is indeed the cause of the hemifacial spasm of our patient, as it is the only abnormal finding of the neuroimaging studies performed. Furthermore, we did not find compression of the nerve at other levels where it is more often encountered, as is the caudal aspect of the VII cranial nerve next to the pons.

Moreover, it is evident that the hemifacial spasm will reappear or recur. For this reason,

the patient is receiving local botulinum toxin, with an excellent response. This treatment was chosen because its secondary effects are scarce and limited in time, and it is beneficial for a great proportion of patients. Also, systemic complications have not been described.[2] Undoubtly, it is a symptomatic treatment based on the blockade of neuromuscular transmision. With respect to surgery, microvascular decompression is an excellent treatment when it is performed by an experienced team,[3] although it poses potential complications and sequelae. Many patients, as in our case, are not willing to undergo such risks. For these reasons, we think that the treatment of choice in our patient is local injection of botulinum toxin.

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Measuring the rate of progression and estimating the preclinical period of Parkinson's disease with [^{18}F] dopa PET

Morrish *et al*[1] report in great detail the PET data on 32 patients with Parkinson's disease, from which they conclude that the mean preclinical period "is unlikely to be longer than 7 years". This conclusion is based on calculations using the [^{18}F] dopa influx constant (Ki) of the putamen, although they acknowledge that other methods of analysis and extrapolation yielded estimates of anything between 2.8 and 37.2 years. The authors justify using putamen Ki because it was "more sensitive to increasing disability" than either total striatal assessment or using the alternative ratio approach, but fail to justify a much more fundamental and unwise assumption on which their arguments rest—that is, the intercorrelation between the PET index, clinical progression, and the UPDRS.

The paper gives little detail about how the UPDRS was administered, presumably only once, before each of the two PET scans an average of 18 months apart. A linear regression was then applied to the mean of each patient's two UPDRS and PET assessments, the gradient of which was expressed as a percentage change in the PET index for a change of 10 points "in the total UPDRS".

Some questions can be raised:

(1) Did the same observer administer the UPDRS blinded to the clinical diagnosis, on their 16 normal controls as well as to each patient on both occasions and, if not, was interobserver reliability studied?

(2) Presumably the "total UPDRS", judging by the scale shown on their figure A, was actually the total score from the 14 items in the motor subset of the UPDRS, which measures impairment rather than disability.

(3) The UPDRS is neither a perfect nor a linear scale. Indeed two coauthors of this paper have pointed out elsewhere the low interrater reliability in some items and redundancy in others.[2] It is a composite multi-item index of severity of disease, each item being an ordinal rather than an interval 0–4 scale of one clinical feature. The key distinction is that an ordinal scale permits the recording of data in rank order (for example, mild, moderate, severe) but without uniform intervals. Thus tremor score 4 is not twice as bad as 2, still less a total motor UPDRS score of 40/70 *v* 20/70. For these reasons, the use of simple arithmetic means as well as other parametric statistical methods is inappropriate, however tempting.

One illustration of the non-linearity of the UPDRS manifest to anyone who has used it regularly in clinical trials is the bias towards intermediate scores. Those with advanced disease and high scores are seldom if ever recruited, and some of the items scored as 1, indicating slight or mild impairment, "could be normal for some" according to the definition. In one study of Alzheimer's disease, 56% of 78 cases and 12 of the 20 age matched controls were found to have isolated extrapyramidal signs with motor UPDRS scores of 4.5 (± 4.8) and 2.8 (± 1.8) respectively using observers not blinded to the diagnosis.[3] It would be interesting to know whether a UPDRS score>0 is sensitive to or predictive of preclinical parkinsonism and/or abnormal PET.

Furthermore, as it is acknowledged that Parkinson's disease may progress at varying rates between patients and possibly within the same patient at different ages and stages, it is perhaps not surprising that the authors found no significant correlation between change in UPDRS and change in any PET index over 18 months. Thus it seems unwise to draw such firm conclusions based on the assumption that both measures are linear and directly correlated.

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1 Morrish P, Rakshi JS, Bailey DL, *et al*. Measuring the rate of progression and estimating the preclinical period of Parkinson's disease with [^{18}F] dopa PET. *J Neurol Neurosurg Psychiatry* 1998;**64**:314–19.
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Morrish replies:

We thank Hardie for his comments but are surprised that he finds difficulty in our assumption of a relation between PET index, clinical progression, and the UPDRS. Whether clinical severity is measured by UPDRS, bradykinesia scores, rigidity scores or Purdue pegboard scores[1 2] such a relation has been a consistent finding in [18F]dopa PET imaging studies of Parkinson's disease. The UPDRS was administered on 57 of 64 occasions by one observer (PKM) and on seven occasions by a second observer (JSR). UPDRS scoring was not carried out on the normal volunteers. Gonera *et al* have identified some non-specific symptoms that may predate the development of Parkinson's disease[3] but we know of no population study of the predictive value of UPDRS score in normal subjects. By total UPDRS score we mean the combined scores of sections I, II, III, and IV. Similar results were found when motor scores alone were examined.[4] The UPDRS scale is the most widely used index of global disease severity in Parkinson's disease. We accept that a linear correlation between UPDRS and PET index may have been inappropriate. The PET index represents a figure of mean [18F] dopa metabolism throughout the putamen, caudate, or total striatum whereas the clinical presentation and severity of parkinsonism is likely to depend on the distribution and severity of loss of dopaminergic function (and that of other neurotransmitters) within and outside the basal ganglia. It is unlikely that the relation is so simple yet this approach has allowed the demonstration of an aspect of the measurement of progression by PET that has not previously been considered, that of sensitivity to clinical severity. It should be noted that this discussion is not relevant to the major findings of the study (that measurement of progression is dependent on the PET method and that the average preclinical period is likely to be short), only to our explanation of these findings. However, it does suggest an important debate; should clinical indices or functional imaging indices be used independently in studies of progression in Parkinson's disease? When the reproducibility of both measurements is taken into account it is, as Hardie comments, not surprising that we found no significant correlation between change in UPDRS and change in PET index.

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Utilisation and costs of profession care and assistance according to disability of patients with multiple sclerosis in Flanders (Belgium)

In their detailed cost of illness study, Carton *et al* estimate the total annual costs in their population of 5500 people with multiple sclerosis to be ECU 13 106 000 (£8.7m) for ambulatory care and ECU 26 581 000 (£17.7m) for hospital and institutional care.[1]

They have adopted a "bottom up" approach which allows costs to be identified for different levels of disability, a distinct advantage from previous "top down" costs of illness studies.[2 3]

They conclude, as have others,[4] that the costs of multiple sclerosis rise with increasing disability and that the information is useful for cost effectiveness studies.

However, to be useful for such studies, the costs would need further description, in particular we would need to know which costs were fixed, and which were semifixed or nonfixed. In our own institution we know that 40% of the cost of a bed-day is fixed and at most 5% of costs are non-fixed. The remaining costs are semifixed—for example, staff salaries (Robert Hudson, Scottish Health Purchasing Information Centre, personal communication January 1998). The important point is that most of the costs in their paper are probably fixed or semifixed, and interventions to reduce disability are unlikely to have a significant impact on these costs as

described. Nevertheless, their data do allow the cost implications of interferon-β for secondary progressive multiple sclerosis to be assessed, albeit given some gross assumptions. If we assume that the effect of treatment with interferon-β lb for secondary progressive multiple sclerosis[5] is to delay time to a wheelchair by 1 year, we could argue that the cost of disability grade III patients would be postponed for 1 year. Given that the trial data for secondary progressive multiple sclerosis suggest that 12 people require treatment for 30 months to save 1 year of wheelchair use, treating 96 people should produce 8 wheelchair-years avoided. From table 7 the cost for a year in grade II is ECU 122 570 for 24 people (therefore ECU 40 917 for eight people), and the cost for a year in grade III is ECU 298 769 for 22.75 people (ECU 105 061 for eight people). The difference (the marginal cost per grade III year avoided) is ECU 64 144 for eight people (ECU 105 061−ECU 40 917). It costs ECU 3.45m (£2.3m) to treat 96 people with interferon β lb for 30 months, assuming ECU 1200 (£800)/month/patient. The net cost of producing 8 wheelchair free years is ECU 3.38m (£2.25m)(ECU 34 500 000−ECU 64 144) . The cost per wheelchair free year is thus ECU 42 2500 (£28 1000).

It is interesting that to offset the costs of disability entirely a drug of similar effect to interferon β lb in secondary progressive multiple sclerosis would need to cost ECU 64 144 for 30 months of treatment for 96 people—that is, ECU 22.27 (£14.83)/patient/month— assuming that all costs as described are in fact avoided.

The study by Carton *et al* has limited value as a stand alone exercise. However, further exploration of the data, as above, leads to the conclusion that disability is expensive to treat, although it is clear that if neurologists are going to prevent disability it will have a price, and it would be naive to suggest that a drug with such an effect will pay for itself.

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1 H Carton, R Loos, J Pacolet, *et al*. Utilisation and costs of profession care and assistance according to disability of patients with multiple sclerosis in Flanders (Belgium). *J Neurol Neurosurg Psychiatry* 1998;**64**:444–50.
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BOOK REVIEWS

Erratum

The author of the book review on **Handbook of Neurologic Rating Scales** published in *J Neurol Neurosurg Psychiatry* 1998;**65**:615 should have read Derick Wade, not Derick White.

An Atlas of Parkinson's Disease and Related Disorders. Edited by G DAVID PERKIN. (Pp 95, £48.00, US$85.00). Published by Parthenon Publishing, Lancashire, 1998. ISBN 1-85070-943-2.

This atlas has three parts, the first a 16 page summary of Parkinson's disease and related disorders, the second a selected bibliography, and the third 77 colour and black and white plates. The text section comprises a brief pathological description of each disorder followed by a clinical description and then treatment and imaging findings if appropriate. The bibliography contains 37 papers mainly published between 1987 and 1996—a golden age of movement disorders? The illustrations are about a third pathological, a third imaging (including CT, MRI, and functional imaging), and a third clinical. The book is aimed at neurologists in training and medical students.

The excellent illustrations, particularly the pathological ones, are the outstanding feature of the atlas. The plates are large and the quality of reproduction good. However, I would have expected rather more pictures in an atlas—many ordinary textbooks have more than 77 figures and quantity as well as quality is desirable. The quality of the captions is variable, the pathological plates are well described but the functional imaging captions are not adequate to interpret the pictures. Similarly most abnormalities in the pathological and structural imaging plates are indicated on the plates but the abnormalities on the functional imaging plates are not.

The text provides a brief overview of the specialty and is a useful introduction. The text is lucid and informative. I thought that the section on striatonigral degeneration, olivopontocerebellar atrophy, and multiple system atrophy would have benefited from further editing to make their interrelation clearer and to ensure consistency between text and tables.

I would recommend this atlas for medical school and hospital libraries. The neurologist in training and neurologist would certainly benefit from perusing the atlas in the library but might choose to start saving for a CD-ROM version.

JERRY BROWN

Clinical Neurology. Second Edition. Edited by C DAVID MARSDEN and TIMOTHY J FOWLER. (Pp 448, £27.50). Published by Edward Arnold, London, 1998. ISBN 0-340-69611-X.

I bought the first edition of this popular book in 1989, shortly after it was published. I dipped into it enthusiastically for a few months, even scribbling some notes in the margins. However, since 1990 it has been unopened. The reason for this neglect is not its content, but rather its presentation. The dense text is relieved by few illustrations and the paragraph headings are too uniform in style to easily understand the chapter structure. These may be superficial criticisms, but they are sufficient to blunt success in the highly competitive market place of neurology text books for students and junior doctors.

This second edition could not be more different. It is beautifully organised. From the original text, clinical bon mots have been highlighted and long paragraphs have been broken up in to plain and boxed text. The introductory chapter on examination of the nervous system is particularly helpful; for instance, Marsden distinguishes between hard and soft neurological signs and describes how to deal with conflicts between them. The scope is wide, including chapters on paediatric neurology and the neurology of general medical disorders, psychiatry, and neurorehabilitation. There is plenty for the Gower's Round hack too: the differential diagnosis of progressive myoclonic ataxia, the subtypes of neuronal ceroid lipofuscinoses, and such favourites. All these were there in the first edition but, at least to my taste, hard to access. For the first time ever, I find myself preferring a sequel.

ALASDAIR COLES

The Management of Pituitary Tumours. Edited by M POWELL and S L LIGHTMAN. (Pp 238, £29.50). Published by Churchill Livingstone, Edinburgh 1997. ISBN 0443060231.

The editors have sought to create a user friendly handbook for the trainee in the specialties that treat these disorders and have succeeded admirably. They give the view of the joint pituitary clinic at the National Hospital, Queen Square, which mirrors the consensus guidelines published recently by the Royal College of Physicians. It is essential that pituitary tumours are managed by a multidisciplinary team—the days of competition between the disciplines should be past. The authors are not afraid to tackle the difficult issue of subspecialisation. There is only sufficient workload for one neurosurgeon in any region of 2-3 million to look after the microadenomas, invasive macroadenomas, giant adenomas, craniopharyngiomas, and third ventricular tumours. Only endocrinologists and neurologists with a specialised interest in neuroendocrinology should he managing the endocrine problems of pituitary patients beyond the initial diagnosis. Have you heard the story of the eminent neurologist who could not understand why a young lady's prolactin level continued to rise despite escalating doses of bromocriptine until all was revealed during the third trimester!

The transatlantic authorship covers the subject in 11 readable chapters devoted to pathophysiology, clinical and visual assessment, imaging, medical and surgical management, radiotherapy, miscellaneous lesions, and controversial issues. The imaging section is particularly useful for explaining the findings of MRI. The sections on results and third ventricular tumours are a little too brief.

This handbook is complimentary to the much larger, definitive textbook published also by Churchill Livingstone—*Pituitary Adenomas*— by Landolt, Vance, and Reilly (1996). I recommend both unreservedly to their respective audiences.

JOHN PICKARD